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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,370	02/21/2001	Etsuro Ogata	OGATA4	9907

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EXAMINER

HARRIS, ALANA M

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 07/15/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/763,370

Applicant(s)

OGATA ET AL.

Examiner

Alana M. Harris, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-6, 8-17 and 19-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-6, 8-17 and 19-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Response to Amendment

1. Claims 2-6, 8-17 and 19-24 are pending.
Claims 6, 16 and 17 have been amended.
Claims 7 and 18 have been cancelled.
Claim 19-24 has been added.
Claims 2-6, 8-17 and 19-24 are examined on the merits.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections

Claim Objections

3. Claim 6 is no longer objected to because it has been amended to correct the misspelled word "metasasis".
4. Claim 18 is no longer objected to because it has been cancelled.

Withdrawn Rejection

Claim Rejections - 35 USC § 112

5. The rejection of claims 2-6, 13, 16 and 18 set forth in Paper number 13 mailed October 22, 2002 under 35 U.S.C. 112, second paragraph, as being indefinite for failing

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to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Claims 7 and 18 have been cancelled.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 2-6, 8-17 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing metastasis of malignant tumor to bone using osteocalcin and bone alkaline phosphatase (BALP), does not reasonably provide enablement for diagnosing metastasis of malignant tumor to bone using any other osteoclast or osteoblast marker, nor a method of evaluating the therapeutic efficacy of a drug using a marker that reflects osteoblast and osteoclast activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants have set forth Examples 1 and 2 on pages 11-14 in which a crossover index was calculated using two markers, osteocalcin and bone alkaline phosphatase (BALP). Results from the two examples yield comparatively low values for patients in which the disease has seemed to progress and greater values for patients in complete remission. Applicants submit that "[i]t can ...be concluded that the crossover index allows for both diagnosis of the progression of bone metastasis and evaluation of drug efficacy in the treatment of bone metastasis." The claims note that the first marker is associated with osteoblasts and the second marker is associated with osteoclasts. The

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specification lists a number of markers associated with both sets of bone metabolic markers, see Table 1 of page 2. The specification does not provide sufficient evidence that other markers commensurate with activity of osteoblasts and osteoclasts such as C-terminal propeptide (PICP) and serum C-terminal telopeptide (ICTP), respectively would yield correlative results. There is insufficient guidance providing that one of ordinary skill in the art could arbitrarily select one of the many osteoblast activity markers and osteoclast activity markers and arrive at a number which is qualitatively commensurate with values obtain using the osteocalcin/BALP index.

Example 3 found on pages 15 and 16 of the specification suggest that the level of serum C-terminal telopeptide (ICTP) is increased comparatively to the ICTP values of patients in the partial response and no change groups. Patients within all groups had chemotherapy by a cyclophosphamide, doxorubicin and fluorouracil (CAF) regimen. As claim 8 suggests the method utilizes two markers, however the specification does not provide an analysis of two markers and the determination of a drug's efficiency. Figure 4, as well as the corresponding example in the specification they are both silent in terms utilizing an osteoclast marker and osteoblast marker for a method of evaluating the therapeutic efficacy. The figure provides the level of ICTP. The disclosure states that BALP was measured, however there was "[n]o statistically significant difference in the values of BALP and CA 15-3" and "[i]t [was] therefore concluded that by measuring the ICTP level on can evaluate the degree of exacerbation of cancer metastasis to bone.", see page 15, lines 22-24; page 16, lines 13-17. Evidently Applicants concluded that one marker was sufficient in the evaluation of the therapeutic efficacy of the CAF

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regimen. There is insufficient guidance providing the use of two markers for the purpose of evaluating the therapeutic efficacy of a drug.

Based on the analysis set forth above there is insufficient evidence provided attesting that the use of one of the five osteoblastic markers and any of the seven osteoclastic markers would yield the same endpoint allowing the diagnosis of bone metastasis and evaluation of therapeutic efficacy of a drug. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to use the claimed methods in a manner reasonably correlated with the broad scope of the claims. Without sufficient guidance the diagnosis of metastasis and evaluation of therapeutic efficacy of a drug is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

7. Claims 2-6, 8-17 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2-6, 20-22 and 24 are vague and indefinite because it is not clear if the first marker or second marker is A or B and the method steps are not clear.

Independent claim 6 sets forth two markers, the first reflects osteoblast activity, wherein the second reflects osteoclast activity. However, dependent claim 20 only lists markers associated solely with osteoblast activity. Likewise, dependent claim 21 sets forth, A is an osteoclast marker and B lists both osteoblast and osteoclast markers. Applicants are requested to discriminately review all claims and ensure clarity.


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b. Claims 8-17, 19 and 23 are vague and indefinite because it is not clear from the claims how the two markers are used in ascertaining therapeutic efficacy of a drug and the method steps are not clear. While it notes that one marker represents osteoclast activity and the other is for osteoblast activity how is these values are to be used is not expressed in the claims. Furthermore, dependent claim 17 presents a ratio wherein A is a osteoclast make. The list for what is B comprises both osteoblasts and osteoclast markers. Applicants are requested to discriminately review all claims and ensure clarity.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER


Alana M. Harris, Ph.D.
July 12, 2003